CA125. CT scan results were generally concordant with CA125 status. No relationship was seen between clinical benefit and HLA type.
Conclusions: Study treatment was well tolerated. There was clear evidence of clinical benefit for some pts, including pts who were heavily pre-treated. This DC-MFP approach warrants further study in patients ovarian carcinoma.
Supported by grants from PrimaBiomed Ltd.

References

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5013 POSTER

Squamous cell carcinoma antigen level as a prognostic factor for uterine cervical carcinoma from Korean Patterns of Care Study 1998–1999

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Background: The aim of this study is to verify prognostic factor of initial serum squamous cell carcinoma (SCC) antigen level as a tumor marker for uterine cervical carcinoma patients with squamous cell carcinoma histology. All the patients received radical radiotherapy and the data were collected from web-based Korean Patterns of Care Study (PCS) 1998–1999 program.
Materials and Methods: We conducted a nationwide on-line data entry of uterine cervical cancer after completion of web-based Korean PCS program (http://www.pcs.re.kr) Of the whole 42 hospitals operating at that time (1998–1999 year) 33 institutions participated the study. Selection of the patients in each hospital was based on randomized sampling process. External audit of the on-line record was reviewed and confirmed by trained central data manager visiting each hospital. The data of 647 patients were reviewed and 400 patients underwent serum SCC antigen level evaluation at diagnosis. We analyzed the treatment outcome of the patients according to SCC level.
Results: The median age of the 400 patients was 61 years old (range 28−86) and 55% (210 patients) of the patients were FIGO stage IIB. Pre-treatment serum SCC antigen level were in the range of 0.1–369 ng/ml. The positivity rate (2.0 ng/ml or more) was increased with FIGO stage. Number of the patients with normal SCC was 115, mild elevation (2.0−4.9 ng/ml) 105, moderate (5.0−19.9 ng/ml) 116, and severe 64. After radiotherapy, 91% of patients with the elevated SCC level were normalized. Thirty five patients developed locoregional relapse and 73 patients had distant metastasis as first event during follow-up period. The 5 year relapse free survival rate (5YRFSR) for FIGO I, II, III, and IV were 92.1%, 61.5%, 31.0%, and 30.0% respectively. The 5YRFSR according to SCC level were 74.5% for normal, 64.1% for mild elevation, 47.0% for moderate elevation, and 58.6% for severe elevation ($p = 0.0005$). By multivariate analysis, initial SCC level was still a prognostic factor ($p = 0.022$).
Conclusions: initial SCC assay is a useful aid to predict the prognosis of squamous cell carcinoma of the uterine cervix. For patients with moderate to severely elevated SCC level (>5.0 ng/ml), more aggressive treatment including higher radiation dose and/or intensive concurrent chemotherapy is needed for better disease control. We recommended that SCC antigen assay and monitoring during follow-up is necessary from the results of Korean PCS 1998–1999 for uterine cervix cancer.

5014 POSTER

Evaluations on the natural history of human papillomaviruses infections and related diseases in HIV-seropositive women

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Background: Convincing evidence has been accumulated that human papillomaviruses (HPV) are the most important risk factor for cervical carcinogenesis also in women infected with human immunodeficiency virus (HIV-seropositive). So far, long-term follow-up of patients with bordeline changes has been difficult to achieve. Thus, the see-and-treat management paradigm was used. Introduction of highly active antiretroviral therapy (HAART) allow a longer patient survival and a more detailed analysis of opportunistic pathologies HIV-associated.
We documented the impact of HAART on the natural history of HPV infections testing specimens by polymerase chain reaction (PCR) with two pairs of primers (MY09/MY11 and GP5*/GP6*) and DNA sequencing.
Material and Methods: From September 2002 throughout January 2005, 379 patients were enrolled at the University of Brescia. Cases are selected at preliminary gynaecological visit as low-grade abnormality. The patients were followed-up by cytology and colposcopy at 6 months intervals and referred for biopsy in cases of persistent or increasing abnormalities. All women had PCR tests at 0, 6, 12, 24, 36 months and a colposcopic-directed biopsy at the endpoint.
Results: At baseline, cytological diagnoses showed 182 smears (48%) within normal limits, 109 ASCUS (29%), 68 low-grade SILs (18% LSIL) and 20 high-grade SILs (5% HSIL). The median CD4 cell count at inclusion was 250/mm^3. The overall HPV DNA high-risk positivity detected was 73% by PCR in the categories of ASCUS/LSIL/HSIL and 12% in the normal specimens. After 1 year, 199 HIV-patients were lost, in the remaining 180 women, the high-risk DNA positivity was maintained in the 58% of samples while 12 patients (7%) showed a cyto-histological progression. In the 110 patients followed-up at 24 months the overall HPV positivity was 52% and 13 showed a cyto-histological progression to high-grade neoplasia. At the end-point only 15 of 105 women (14%) had biopsy-confirmed CIN3.
Conclusions: Nowadays, timely treatment by HAART confers a substantial improvement in curative potential and live cost savings of patients. Meanwhile higher reliability of PCR techniques has substantially increase the detection rate of incoming HPV infections with acceptable positive predictive values. Our studies revealed that HAART modified the course of CIN in HIV-infected women by significantly reducing HPV positivity and increasing the reversion of the low-grade abnormality to normality. Fine data on the impact of HAART on the different cervical HPV lesions will be presented.
This study was funded by AIRC programme 2001 and by Ministero della Salute, Programma per la Ricerca Sanitaria 2003.

5015 POSTER

The usage of expression profiles of p53, delta Np63, and delta Np73 as prognostic markers in invasive cervical carcinoma

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The tumor-suppressor protein p53 has been shown to belong to a family that includes two structurally related proteins, p63 and p73. In contrast to p53, p63 and p73 encodes truncated N-terminal isoforms of p63 (delta Np63) and p73 (delta Np73) which can inhibit the transactivating function of full length isoform. In this study, we investigate the correlation between the inactivation of p53 protein via the presence of oncogenic viral E6 and the overexpression of delta p63/p73 isoforms in 33 invasive cervical carcinoma. Overexpression of p14 and p16 will be used as indicators for the inactivation of p53 and pRb by HPV oncoprotein E6 and E7. Immunostaining of p14, p16, delta Np63 and delta Np73 will be compared to the cervical staging and HPV status using 20 normal cervix as control. Overexpression of p14, p16 delta Np63 and delta Np73 are statistically increased comparing to normal cervix with p value (Mann-Whitney test) of <0.001, <0.001, 0.002 and <0.001, respectively. Our results clearly showed that overexpression of p14 and p16 is well correlated to the presence of integrated HPV, while negative staining was found in normal cervix. Interestingly, inactivation of p53 protein was found to correlate with up regulation of delta p63 ($p < 0.001$) but not delta p73 (0.454). Moreover, expression profiles of p14, p16, deltaNp63, and deltaNp73 demonstrated statistically associated with clinical staging using Mann-Whitney test at $p < 0.001$, $p < 0.001$, $p = 0.004$ and $p < 0.001$, respectively. Our study suggested that loss of functional p53 protein might enhance p63 expression leading to increase deltaNp63 isoform. Outcome of the followed-up cases will also be analyzed in order to evaluate its possible potential as prognostic profile in cervical cancer treatment.

5016 POSTER

A prospective study of MR imaging prognostic factors in women with cervix cancer treated with chemo-radiation

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Purpose: Chemo-radiation (CRT) has become the standard of care in women with locally advanced cervix cancer. The use of MRI as part of the staging investigations makes it possible to accurately estimate the volume and relations of the tumor, as well as the presence of lymph nodes. Further improvements in patient outcome will depend on a better understanding of the causes of pelvic and systemic relapse and the use of predictive prognostic factors to individualize treatments. The knowledge of these factors through modern imaging could be used for selecting the optimum treatment modality while minimizing side effects.

This study is aimed to determine the impact of MRI features such as tumor volume, myometrial invasion and extent of nodal involvement in the outcome of patients with locally advanced cervix cancer treated with CRT.
Materials and Methods: 97 patients underwent exam under anesthesia and had MRI staging investigations prior to entry in a prospective study of CRT between 1999 and 2006. Characteristics of the patients are as follows: median age was 52 years, FIGO stage was IB/IIA in 38, IIB in 32, IIIA/B in 21, and IVA in 6 patients. Tumor characteristics were assessed as follows: clinical tumor size, tumor size by imaging, tumor volume by imaging, depth of myometrial extension >2 cm vs. <2 cm. The number of lymph nodes at MRI were classified as: number of nodes >5 mm, number of nodes >8 mm, number of nodes >10 mm, and maximum nodal diameter, measured along the shortest dimension. Pelvic radiation was given to a dose of 45−50 Gy in 25 fractions followed by 40 Gy using LDR or PDR brachytherapy. Weekly cisplatin was given at a dose of 40 mg/m^2 for 5 courses.
Results: After completing CRT treatment 77.5% of the patients had complete response. The disease free survival (DFS) at 3 years was 53%. In the multivariate analysis of tumor characteristics the depth of myometrial invasion >2 cm was the strongest predictor of DFS (HR 3.42, 95% CI 1.82−6.45, p = 0.00014) when compared to the other tumor variables. The multivariate analysis of lymph node characteristics showed that the maximum nodal diameter, as well as the number of nodes were important predictors for DFS. When these three variables were analysed together only myometrial invasion >2 cm and number of lymph nodes >8 mm were predictors of DFS (HR 2.93, 95% CI 1.44−5.95, p = 0.0029, and HR 1.24, 95% CI 1.09−1.40, p = 0.00069 respectively)
Conclusions: Depth of myometrial invasion measured using MR imaging appears to be a better predictor of DFS than tumor volume in women with locally advanced cervix cancer.
The number of enlarged nodes adds significant prognostic information above that provided by diagnosis of nodal involvement alone. These results are consistent with data from surgical staging in cervix and other cancers, may improve prognostication and treatment selection, and demonstrate the importance of MR imaging in the staging of these tumors.

5017 POSTER

p70S6K induces epithelial to mesenchymal transition in human ovarian cancer cells through upregulation of Snail

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Background: Epithelial ovarian cancer is the most lethal gynecological malignancy and is a highly metastatic cancer characterized by widespread peritoneal dissemination and ascites. The 70 kDa S6 kinase (p70^{S6K}) is a downstream effector of the phosphatidylinositol 3-kinase/AKT/mTOR pathway, which is frequently activated in human ovarian cancer. We recently demonstrated a novel role of p70^{S6K} in the invasion of ovarian cancer cells. Since epithelial-to-mesenchymal transition (EMT) is a critical step contributing to tumor invasiveness, we hypothesized that p70^{S6K} activation induced molecular alterations that mediate EMT.
Materials and Methods: To examine the roles of p70^{S6K}, constitutively active forms of p70^{S6K} were transfected into the ovarian cancer cell lines, and the consequence of their transfection was investigated. Optical microscopy was used to assess changes in cell morphology and behavior. Western blot, reverse transcription (RT)-PCR, and reporter gene assays were employed to measure the expression and activity of epithelial and mesenchymal markers.
Results: We showed that ovarian cancer cells expressed constitutively active p70^{S6K} underwent phenotypic changes consistent with EMT: the cells lost epithelial cell morphology, acquired fibroblast-like properties, and showed reduced intercellular adhesion. Western blot and RT-PCR revealed strong reduction of the epithelial marker E-cadherin expression and activation of mesenchymal markers vimentin and N-cadherin in p70^{S6K}-expressing cells. Consistently, p70^{S6K} downregulation by small interfering RNA (siRNA) or the specific mTOR/p70^{S6K} inhibitor rapamycin caused the reversion to an epithelial phenotype, in which E-cadherin was relocalized to the plasma membrane. In addition, active p70^{S6K} induced upregulation of Snail, a repressor of E-cadherin and an inducer of the EMT, which could be reverted by siRNA-mediated repression of p70^{S6K}, indicating that p70^{S6K}-induced EMT depends on Snail. We also showed that p70^{S6K} enhanced Snail activity through inactivation of glycogen synthase kinase 3beta (GSK3β), as expression of constitutively active GSK3β blocked p70^{S6K}-dependent Snail activation.
Conclusion: Our study indicates, for the first time, that activation of p70^{S6K} mediates EMT through upregulation of Snail via GSK3β. These findings not only expand the spectrum of biological activities of p70^{S6K} but also suggest that therapeutic inhibition of p70^{S6K} may be a useful strategy to control ovarian tumor invasion and metastasis (supported by RGC HKU7599/05M).

5018 POSTER

p53 dominant-negative mutant R273H promotes invasion and migration of human endometrial cancer HHUA cells

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Background: Dominant negative (DN) mutations of tumor suppressor p53 (TP53) are clinically associated with cancer progression and metastasis of endometrial malignancy. In this study, we used human endometrial cancer cells HHUA expressing wt p53, to clarify the role and mechanism of DN mutants of p53 in endometrial tumorigenesis.
Materials and Methods: We generated cells that stably co-expressing wt p53 and R273H DN mutant p53 (273H cells) and cells stably co-expressing wt p53 and R213Q recessive mutant p53 (213Q cells). Their invasion and migration capabilities were compared with parent HHUA cells. We also assessed the expression of wt p53 target genes Maspin, PAI-1 and KAI1 in these cell lines. Moreover, induction of wt p53 function by Adriamycin and stable expression of R273H in p53-null SK-OV-3 and Saos-2 cells were used to determined whether R273H functions as a gain-of-function mutant, contributing an invasive phenotype in HHUA cells.
Results: 273H cells showed markedly increased invasion and migration potentials, and displayed reduced Maspin, PAI-1 and KAI1 mRNA expressions as compared with 213Q and parent cells. The wt p53 induction by Adriamycin resulted in the inhibition of the invasion capacity in association with the up-regulation of Maspin, PAI-1 and KAI1 to a far greater degree in 213Q and wt cells than in 273H cells. R273H expression in SK-OV-3 and Saos-2 cells did not significantly affect cell invasion activities.
Conclusions: Our results suggest that DN mutant TP53 R273H may promote endometrial metastasis by increasing invasion and migration of tumor cells through the mutant p53 transdominance mechanisms.

5019 POSTER

Growth inhibition and FAS-mediated apoptosis in human endometrial cancer cells by treatment with isoliquiritigenin (ISL)

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Background: Endometrial Cancer is the 3rd most common gynecologic malignancies in Korea. Despite the fact that endometrial cancer is so common, innovative research has traditionally been lacking. Isoliqiritigenin(ISL) is a calchone flavonoid, present in licorice, shallot and bean sprouts, has cancer-preventing properties and often used in Oriental medicine. ISL is one of components in Spatholobus subrectus Dunn in the literature. In the present study we used ISL to determine its effect on cell proliferation and cell cycle progression in human endometrial cancer cell line, HEC1-A.
Materials and Methods: Endometrial cancercells(HEC-1-A) were treated with ISL. Cell viability analysis was analyzed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTS) assay and Flow cytometry was performed to ascertain the effects ISL. Expression of cell cycle related proteins and apoptosis related proteins were evaluated by Western blot analysis.
Results: Cell viability was significantly influenced by ISL treatment in a dose-dependent manner. Flow cytometry results showed that ISL induced Sub G1 and G2/M arrest. To reiterate this observation, DNA fragmentation assay was carried out and apoptosis was detected. Activation of caspase-3 and caspase-8, down-regulation of Bcl-2, with concomitant increase in Bax and FAS was observed. ISL treatment of endometrial cancer cells resulted in a concentration-dependent cell death induced via the FAS receptor-apoptosis cascade mechanism.
Conclusions: These results suggest that ISL treatment in endometrial cancer cells leads to growth inhibition and that this inhibition is mediated at least in part by apoptosis via the FAS death receptor induced caspase-8 cascade pathway. These results suggest that ISL will be a promising agent for use in chemopreventive or therapeutics against human uterine endometrial cancer.